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Previews

Untapping the Potential of Human Retinal Pigmented Epithelial Cells

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The innate capacity of adult somatic cells has many potential applications in regenerative medicine. In this issue of *Cell Stem Cell*, Salero et al. (2012) describe an adult retinal stem cell population capable of generating neural and mesenchymal cell lineages.

Age-related macular degeneration (AMD) is the leading cause of blindness in people over the age of 60 in the western world, and each year the number of affected people increases. AMD results in the central portion of vision being lost, making it impossible to appreciate fine detail. About 25% of people over 60 in the UK have some degree of visual loss due to AMD and it is estimated that between 12 and 15 million people are affected by this disease in the USA alone. AMD is therefore a significant global healthcare problem. In an exciting new paper in this issue of *Cell Stem Cell*, Temple and colleagues describe an adult stem cell population in the retinal pigment epithelial (RPE) cells that may provide a source of cells for treating this disease (Salero et al., 2012).

AMD is associated with defects of the retinal support cells—the RPE cells. The rods and cones (the photoreceptors) in the retina, which are the light-sensitive cells, depend on the RPE for their survival, so RPE failure leads to progressive loss of vision. To make matters worse, the disease often provokes a scarring process at the back of the eye, leading to the formation of new blood vessels within the retina (choroidal neovascularization, CNV) that subsequently leak fluid, resulting in exudative AMD or so called "wet" AMD. The retina is very intolerant of this scarring and rods and cones are lost at a greater rate, leading to a more dramatic loss of vision. This exudative form of AMD occurs in 10% of AMD patients, but is responsible for 90% of cases of severe visual loss. AMD without the neovascular component is referred to as geographic atrophy or "dry" AMD. Replacement of RPE cells (Coffey et al., 2002) or their translocation from the peripheral retina is a viable treatment for AMD, if surgical intervention occurs at an appropriate time (da Cruz et al., 2007). However, at present, availability of suitable donor cells and the time involved for the necessary complicated retinal surgery means that these treatments can only be made available to a very small proportion of patients. Stem-cell-based approaches therefore have great therapeutic potential for presently untreatable degenerative diseases such as AMD.

In their paper, Salero, Blenkinsop, and colleagues present important new data demonstrating that the adult human RPE contains a subpopulation of multipotent RPE stem cells (RPESCs) that can be activated to self-renew in vitro and differentiate to give rise to neural and mesenchymal progeny. Although RPE cells do not proliferate in situ, these findings suggest that RPESCs may contribute to repair or pathological differentiation under conditions of injury and degenerative disease.

To conduct their study, the authors obtained eye samples from human donors spanning a wide age range. They found that RPE isolates grew robustly in adherent conditions at similar growth rates, independent of the age of the donor, to produce confluent cobblestone monolayers expressing RPE markers. A fraction of the RPE cells self-renewed, as demonstrated by their ability to form spheres that could be serially propagated and clonal analysis. Salero, Blenkinsop, et al. next found that the cobblestone

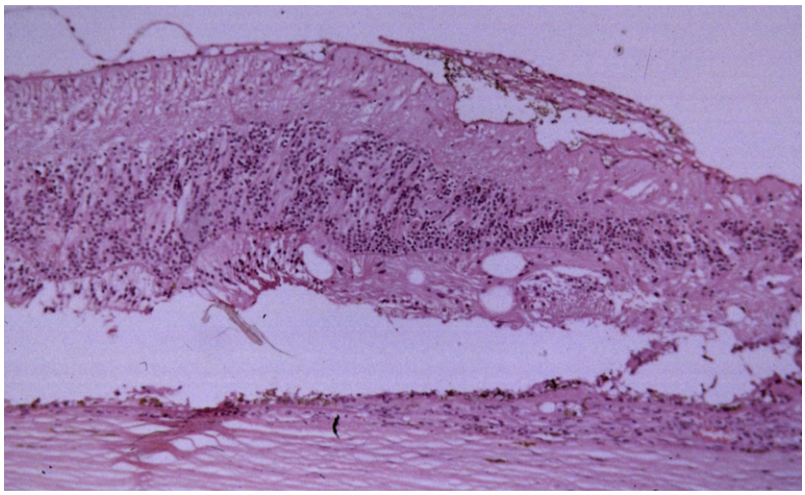

Figure 1. VPR Is a Disease that Develops as a Result of a Tear in the Retina
Vitreous humor leaking into the retinal hole contains cytokines that activate the RPE. As a result, RPE cells proliferate and migrate out into the vitreous compartment to form a fibrotic scar (image courtesy of Dr. Philip J. Luthert, UCL). The findings from Salero, Blenkinsop and colleagues suggest that the RPESC population could be the cell of origin for VPR.

monolayers could be induced to undergo cell fate transitions. Growth in neural differentiation medium caused the cells to acquire an anterior/eye field progenitor marker profile and suppress expression of the RPE marker MITF. Surprisingly, the authors also found that growth in media promoting differentiation toward mesenchymal lineages resulted in expression of markers consistent with adipocyte, chondrocyte, and osteogenic phenotypes. To rule out the possibility that these cell types were generated by contaminating mesenchymal cells present in the starting culture, the authors expanded clonal RPESC lines and confirmed that they were capable of generating RPE and mesenchymal progeny. Furthermore, they found that GFP-labeled human RPESCs could also give rise to mesenchymal derivatives in a chick chorioallantoic membrane assay.

Cellular plasticity in the RPE has been regarded primarily as a property of lower vertebrates (Araki, 2007). However, these new findings suggest that adult human RPESCs may hold the potential to undergo complete transdifferentiation to neuroretinal and other phenotypes. As the authors discuss, an innate capacity of the RPE to dedifferentiate in vivo leads to a pathological condition called proliferative vitreoretinopathy (PVR). PVR occurs in the eye when the monolayer of RPE is disrupted, typically by detachment of the overlying neural retina. RPE cells dislodge from their underlying Bruch's membrane and proliferate along a mesenchymal lineage, resulting in a fibroblastic scar (Figure 1). Salero and colleagues were able to recapitulate this phenomenon in vitro, providing an important tool for identifying therapeutics that can inhibit this process. Equally, understanding how dedifferentiation and expansion of RPE cells is regulated may help in other diseases that involve RPE degeneration.

Last but not least, these results provide an important illustration of the reprogramming capacity of not just induced pluripotent stem cells but even adult somatic cells. Salero et al. convincingly show that RPE cells maintain the ability in adulthood to reprogram to become multipotent along a mesenchymal lineage and form precursors of a number of different cell types. They therefore represent an additional source of adult human stem cells.

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Tales From the Crypt: The Expanding Role of Slow Cycling Intestinal Stem Cells

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Similar to other highly self-renewing tissues, the intestinal epithelium contains both slowly and rapidly cycling progenitor/stem cells, though their relationship has been largely unexplored. Two recent reports in *Nature* (Tian et al., 2011) and *Science* (Takeda et al., 2011) shed new light on their dynamic interplay.

The small intestinal epithelium has enormous capacity for self-renewal, replacing itself every 3 to 5 days. The cellular basis for this regenerative potential has long been accepted to reside in multipotent intestinal stem cells (ISCs) (Cheng and Leblond, 1974). Based on the hypothesis that ISCs would be slowly cycling, Potten and colleagues initially employed DNA label retention models to identify these cells. These studies led to the discovery and characterization of putative ISCs located in the "+4 crypt position" (Figure 1) (Potten et al., 1974). While this finding subsequently gave rise to the discovery of a number of additional markers based on colocalization with label retention, functionally validated ISC markers remained elusive for over three decades (reviewed in Montgomery and Breault, 2008).

The first functionally validated ISC marker to be identified was *Lgr5*, a downstream target of canonical Wnt signaling (Barker et al., 2007). In contrast to Potten's original observation, *Lgr5* expression corresponded to crypt base columnar cells, located between Paneth cells at the crypt base (Figure 1), a site previously suggested to contain ISCs (Bjerknes and Cheng, 1999). Surprisingly, and in stark contrast to the label-retaining population, the majority of *Lgr5*-expressing cells were shown to be rapidly cycling, raising doubts as to whether bona fide slowly cycling ISCs were also present in